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SHORT COMMUNICATION

# THE IMMUNOLOGICAL EFFECT OF HIGH-DOSE CHEMOTHERAPY IN MULTIPLE MYELOMA

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The different outcomes of autologous hematopoietic stem cell transplantation (AH SCT) may be due to engraftment with adequate numbers of hematopoietic stem cells, which is determined by bone marrow stromal cells and is significantly impaired by continuous high-dose chemotherapy. Another important factor is immunological reconstitution, which can be influenced by the bone marrow microenvironment<sup>1</sup>.

There is a group of patients with multiple myeloma (MM) who have disease control with a long response time after AH SCT. In general, these are patients who present changes in the bone marrow microenvironment that can maintain an immunological response with antitumor action<sup>2</sup>. Cytoreduction is associated with changes in cytokine production and immunological activation that contribute to subsequent specific immunity with anti-tumor action. Therefore, there are several immunological changes that occur after AH SCT that suggest that long-lasting control of MM occurs for reasons other than just the cytotoxic action of melphalan chemotherapy conditioning<sup>3</sup>.

Studies of patients with MM have demonstrated that T lymphocytes and natural killer (NK) cells become quantitatively and functionally altered in the last stage of the disease. These dysfunctions have been associated with the progression of MM and the reduced number of NK cells, pointing to a role for these cells in controlling the disease<sup>4</sup>. NK cell counts and function recover quickly, usually within 1 month after transplantation. Faster reconstitution

of NK and T cells may contribute to improved clinical outcome<sup>5</sup>.

Melphalan conditioning followed with hematopoietic stem cell rescue results in increased plasma levels of IL-6, IL-7, and IL-15 compared with pre-AH SCT levels in MM patients. CD3 T cells present from the autologous stem cell graft die rapidly when cultured without cytokines in vitro, and therefore addition of IL-7 or IL-15 can induce their survival and proliferation<sup>6</sup>.

High-dose melphalan resulted in a rapid burst of inflammatory cytokines and chemokines during the cellular recovery phase after myelodepletion. After melphalan treatment, tumor cells exhibited features of immunogenic cell death, including translocation of calreticulin into the endoplasmic reticulum membrane. Furthermore, there was an increased uptake of tumor antigens by dendritic cells. Consistent with these immunomodulatory effects, melphalan treatment of tumor-bearing mice led to activation of endogenous CD8 + T cells and, more importantly, effectively drove clonal expansion and effector differentiation of tumor-specific CD4 + T cells. These findings provide insight into the immunostimulating effects of melphalan<sup>7</sup>.

More studies in this area are needed to better understand why there are different responses and survival rates in myeloma patients who undergoing to AH SCT and thus enable a better response to this therapy. In the future, it could help in the development of cellular therapies similar to those carried out in patients with acute myeloid leukemia<sup>8</sup>.

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